REMARKS

By the present amendment, Claims 21, 39, and 40 have been cancelled without prejudice or disclaimer. Claims 23, 26, 28, and 37-38 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional appliactions. Claims 22, 24-25, 27, and 29-36 are currently being examined on the merits.

Exemplary support for the amendments to part (d) of Claim 22 can be found in the Specification at page 7, lines 17-18, and page 15, lines 2-5.

Comments regarding restriction requirement

Claims 23, 26, 28, and 37-38 are "method of use" claims which all ultimately depend from antibody product Claim 22. Therefore, upon allowance of Claim 22, it is believed that Claims 23, 26, 28, and 37-38 should be rejoined and considered, in accordance with the commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103 (b)."

Objection to the Specification:

The Examiner has objected to the specification since the paragraph immediately following the title did not reflect the current priority status of the present application. The paragraph has now been amended accordingly to reflect the same.

Utility rejections under 35 U.S.C. §§ 101 and 112, first paragraph:

The Examiner has rejected claims 22, 24-25, 27, and 29-36 under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific asserted utility or a well-established utility. **The rejection of claims 22, 24-25, 27, and 29-36 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.**

The Examiner erroneously refered to the HUPAP protein as a serine kinase (Office Action, Paper Number 9, page 4). The Specification clearly states that, "HUPAP, a serine

protease which appears to function in the prostate gland, shares chemical and structural homology with bovine enterokinase, human pancreatic kallikrein, and African rat renal kallikrein". (Specification, page 18, 2nd to last paragraph.)

In the present case, the Examiner contended that the degree of amino acid identity among HUPAP and other serine protease family proteins is insufficient to establish that HUPAP is a member of the serine protease family of proteins and thus shares the same utilities. The Examiner attempted to support this assertion with the teachings of Bowie et al. (Science (1990) 247:1306-1310), Lazar et al. (Mol. and Cell. Biol. (1988) 8:1247-1252), and Burgess et al. (J. Cell Biol. (1990) 111:2129-2138), all of record and addressed below. However, all of these references fail to support the outstanding rejections.

Appellants submit that the teachings of Bowie et al. are, in part, counter to the outstanding rejections, and in part, supportive of the asserted utilities of HUPAP based on amino acid sequence homology to serine protease family proteins. Careful review of this reference reveals that the teachings of Bowie et al. are directed primarily toward studying the effects of site-directed substitution of amino acid residues in certain proteins in order to determine the relative importance of these residues to protein structure and function. As discussed below in further detail, such experiments are not relevant to Applicants' use of amino acid sequence homology to reasonably predict protein function.

In support of Applicants' use of amino acid sequence homology to reasonably predict the utility of the claimed polypeptide, Bowie et al. teach that evaluating sets of related sequences, which are members of the same gene family, is an accepted method of identifying functionally important residues that have been conserved over the course of evolution. (Bowie et al., page 1306, 1st column, last paragraph, and 2nd column, 2nd full paragraph; page 1308, 1st column, last paragraph; page 1310, 1st column, last paragraph.) It is known in the art that natural selection acts to conserve protein function. As the Examiner stated and as taught by Bowie et al., proteins are tolerant of numerous amino acid substitutions that maintain protein function, and it is natural selection that permits these substitutions to occur. Conversely, mutations that reduce or abolish protein function are eliminated by natural selection. Based on these central tenets of molecular evolution, Applicants submit that the amino acid differences among Applicant's claimed polypeptide and known proteases are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein

function. One of ordinary skill in the art would further conclude that the level of conservation observed between Applicant's claimed polypeptide and proteases is indicative of a common function, and hence, common utility, among these proteins.

In further support of this assertion, Applicants direct the Examiner's attention to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a dataset of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) As shown in Figure 2 and as reported in the specification, SEQ ID NO:1 and enterokinase share 38% identity over 283 amino acids, thus meeting the criteria of Brenner et al. Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.) SEQ ID NO:1 and bovine enterokinase also meet these criteria, as the region of SEQ ID NO:1 from I196-I275 shows identity to bovine enterokinase at 38 out of 80 residues, corresponding to 47.5% sequence identity. Therefore, SEQ ID NO:1 and bovine enterokinase share sequence identity that exceeds the thresholds proposed by Brenner et al. Thus, SEQ ID NO:1 is a true bovine enterokinase homolog by these criteria. Since these criteria are based on a dataset of homologous proteins with shared structural and functional features, one of ordinary skill in the art would likewise expect SEQ ID NO:1 to possess the evolutionarily conserved structural and functional characteristics of serine proteases. Hence, the "reasonably correlation" standard as set by case law has been met.

The Examiner further cited Lazar et al. and Burgess et al. as demonstrating that "even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein". (Office Action, Paper Number 9, page 5.) However, these references are not relevant to the case at hand. Lazar et al. describe the mutagenesis of two amino acid residues that are highly conserved among EGFs and TGF-αs. Similarly, Burgess et al. describe mutagenesis of HBGF-1 at an amino acid residue known to be important for ligand binding. In both of these cases, particular amino acid residues with known importance to protein function were specifically targeted for site-directed mutagenesis. These mutations were

"artificially" created in the laboratory and, therefore, are **not** analogous to molecular evolution, which is profoundly influenced by natural selection. For example, the deactivating mutations as described by Lazar et al. and Burgess et al. would almost certainly not be tolerated in nature. Furthermore, it is clear that over the course of evolution, amino acid residues that are critical for protein function are **conserved**. Thus, the amino acid differences between SEQ ID NO:1 and bovine enterokinase are likely to represent substitutions that do **not** alter protein function. Therefore, the teachings of Lazar et al. and Burgess et al. are not relevant to the case at hand.

One could then argue that partial loss-of-function mutations do occur in nature, for example, the mutation in hemoglobin that causes sickle cell anemia. However, this example is the **rare** exception in evolution, **not the rule**. Persistence of such a mutation in a population would **not** be expected by one of ordinary skill in the art. Persistence occurs only because of the fluke of heterozygous advantage. Therefore, the Examiner's assertion that one of skill in the art would routinely expect to find single amino acid substitutions that drastically affect the function of the individual members of a conserved protein family is entirely unsubstantiated.

As the cited evidence is completely insufficient to support the rejections of the claims, the outstanding rejections must be withdrawn for this reason alone. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptide is in fact a member of the serine protease family of proteins, which are known to have specific utility.

The Examiner further stated that, "those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression". (Office Action, Paper 9, page 6.) The Examiner then cited various publications in support of this allegation. See, in particular, Alberts et al., Fu et al., and Rama et al. cited at page 6 of the Office Action. The Examiner concluded that thus, the predictability of protein translation and its possible use as a diagnostic are not contingent on the levels of mRNA expression due to a multitude of homeostatic factors affecting transcription and translation. The Examiner stated further that for anti-HUPAP antibodies to serve as clinically relevant diagnostic markers for cancer, the claimed protein must be present only in diseased tissue to the exclusion of normal tissue.

Applicants disagree with the Examiner's allegation that mRNA expression does not

correlate with or predict polypeptide expression in the instant case.

Regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification and protein turnover. While steady state mRNA levels are not always directly proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. The Office Action cites three examples of protein regulation downstream of transcription; however, these examples represent comparatively unusual mechanisms of gene regulation. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (pages attached as Exhibit A):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems... ***For most genes, this is a major control point; probably it is the most common level of regulation.*** [page 847, emphasis added].
>
> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the initiation o transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation.*** [pages 847-848, emphasis added]

Thus the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:1 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:1 expression correlates with the levels of SEQ ID NO:2 mRNA. Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner, thereby dismissing the significance of mRNA levels.

Appellants respectfully reiterate the assertion that mRNA levels are usually a good indicator of protein levels. This suggests that the regulation of genes is at the level of

transcription. While there are examples in the literature of genes that are regulated post-transcriptionally, the authoritative text in the field of molecular biology, Alberts et al.;*The Molecular Biology of the Cell*, which the Examiner has cited in support of his allegation, as well as a wealth of data in the literature indicate that the *predominant* level of control of gene expression is at transcription. For example, in discussing the complicated process of gene expression, Alberts et al. state,

> There are many steps in the pathway leading from DNA to protein, and all of them can in principle be regulated. Thus a cell can control the proteins it makes by (1) controlling when and how often a given gene is transcribed (transcriptional control), (2) controlling how the primary RNA transcript is spliced or otherwise processed (RNA processing control), (3) selecting which completed mRNAs in the cell nucleus are exported to the cytoplasm (RNA transport control), (4) selecting which mRNAs in the cytoplasm are translated by ribosomes (translational control), (5) selectively destabilizing certain mRNA molecules in the cytoplasm (mRNA degradation control), or (6) selectively activating, inactivating or compartmentalizing specific protein molecules after they have been made (protein activity control).
>
> **For most genes transcriptional controls are paramount**...Although all of the steps involved in expressing a gene can in principle be regulated, for most genes the initiation of RNA transcription is the most important point of control." (emphasis added).
>
> (*The Molecular Biology of the Cell*, Alberts B. et al., editors, Garland Publishing, Inc., 1994, 3rd Edition, page 403-404; Exhibit B).

Even in discussing posttranscriptional controls, Alberts et al. state that, "[a]lthough controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made" (Alberts et al., page 453, Exhibit C). Indeed Alberts et al. goes on to describe several examples of genes exhibiting posttranscriptional control, including the example cited by the Examiner at page 465 of the Alberts reference. However, the fact that there are examples of genes that are regulated by posttranscriptional controls, does not detract from the observation that the *preponderance* of genes are regulated at the level of transcription. This, therefore supports Appellants' assertion that mRNA levels are *usually* a good indicator of protein levels, as in the instant case absent evidence to the contrary.

Furthermore, applicants disagree that for the claimed antibodies to "be used as a surrogate for a disease state," the claimed protein must be present in diseased tissue to the exclusion of

normal tissue. As the Examiner has acknowledged, applicants have shown at page 18 of the specification, 2nd to last paragraph, differential expression of the polynucleotide encoding SEQ ID NO:1 (and hence SEQ ID NO:1) in 3/4 patients with prostate cancer. This is sufficient to indicate the presence of cancer and therefore does not require the complete exclusion of the marker in one tissue versus the other.

Applicants therefore submit that for all the above reasons, the specification discloses both a specific asserted utility and a well-established utility for the protein comprising SEQ ID NO:1, and hence, antibodies and methods of making said antibodies to SEQ ID NO:1, and that the skilled artisan would clearly know how to use them for these purposes. Withdrawal of the rejection of claims 22, 24-25, 27, and 29-36 under 35 U.S.C. §§ 101 and 112, first paragraph, is therefore requested.

Written description rejection under 35 U.S.C. §§ 112, first paragraph:

Claims 22, 24-25, 27, and 29-36 have been rejected under the first paragraph of 35 U.S.C. § 112 for alleged lack of an adequate written description.

According to the Office Action, "the written description is not commensurate in scope with the claims drawn to antibodies which bind naturally occurring amino acid sequences having at least 90% sequence identity to the sequence of SEQ ID NO:1, antibodies which bibd a fragment of SEQ ID NO:1..." (Office Action, Paper Number 9, page 8.) This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Attention is drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial

> structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (footnotes omitted.)

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the recited "variants" and "fragments" of SEQ ID NO:1 and antibodies which bind specifically to them

The subject matter encompassed by claims 22, 24-25, 27, and 29-36 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

SEQ ID NO:1 is specifically disclosed in the application (see, for example, page 8, lines 20-25). Variants of HUPAP are described, for example, at page 9, lines 5-7. In particular, the preferred, more preferred, and most preferred HUPAP variants (80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:1) are described, for example, at page 9, lines 5-7. Incyte clones in which the nucleic acids encoding the human HUPAP were first identified and libraries from which those clones were isolated are described, for example, at page 8, line 15-19 of the Specification. Chemical and structural features of HUPAP are described, for example, on page 8, lines 25-31 through page 9, line 1. Fragments of SEQ ID NO:1 having protease activity and immunogenic fragments of SEQ ID NO:1 are described at, for example, on page 6, line 31 to page 7, line 2; page 7, lines 17-18; and page 7, lines 21-22.

One of ordinary skill in the art would recognize naturally occurring amino acid sequences which are variants at least 90% identical to SEQ ID NO:1. Given any naturally occurring amino acid sequence, it would be routine for one of skill in the art recognize whether it was a variant of SEQ ID NO:1. Similarly, SEQ ID NO:1 provides the blueprint to describe any fragment thereof. Accordingly, the Specification provides an adequate written description of the recited variants and fragments of SEQ ID NO:1.

There simply is no requirement that the claims recite particular amino acid "variant" and "fragment" sequences because, as discussed above, the Specification already provides sufficient structural definition of the claimed subject matter. Because the recited amino acid "variants" and "fragments" are defined in terms of SEQ ID NO:1, the precise chemical structure of every amino acid variant and fragment within the scope of the claims can be discerned. Accordingly, the Specification provides an adequate written description of the claimed sequences. The Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention.

1. The present claim specifically defines the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind to the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define antibodies which specifically bind to the polypeptides in terms of chemical structure, rather than functional characteristics. For example, the "variant" and "fragment" language of independent claim 22 recites chemical structure to define the claimed genus:

Claim 22:

22. An isolated antibody which specifically binds to an isolated polypeptide selected from the group consisting of:
a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1,
c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said fragment has protease activity, and
d) an immunogenic fragment of at least 15 contiguous amino acids of a polypeptide having the amino acid sequence of SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides to

which the claimed antibodies specifically bind. Moreover, the functional recitations of "protease activity" and "immunogenic" add to the structural characterization of the fragments to which the claimed antibodies specifically bind. The polypeptide, defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. (Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to antibodies which specifically bind polypeptides related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as prostate-associated proteases and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language"of the present claims recites, for example, a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." This variation is far less than that of all potential prostate-associated proteases related to SEQ ID NO:1, i.e., those prostate-associated proteases having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of February 17, 1997. Much has happened in the development of recombinant DNA technology in the 20 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants and fragments at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of antibodies which specifically bind to the polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and

Fiers cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the above reasons, withdrawal of this rejection is requested.

New matter rejection under 35 U.S.C. § 112, first paragraph

On page 10 of the Office Action, Claims 22, 24-25, 27, and 29-36 were rejected under the first paragraph of 35 U.S.C. § 112 for allegedly containing new matter. By the present amendment, part (c) of Claim 22 has been revised to recite that the "fragment has protease activity." Exemplary support for this amendment can be found in the Specification at page 8, lines 11 to page 9, line 4. Withdrawal of this rejection is therefore requested.

Please charge Deposit Account No. **09-0108** in the amount of **$**_____ as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108.

Respectfully submitted,
INCYTE CORPORATION

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